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DOBE LAW GROUP, LLC
7207 HANOVER PARKWAY
SUITE C/D
GREENBELT, MD 20770

EXAMINER	
SZPERKA, MICHAEL EDWARD	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/026,931
Filing Date: December 27, 2001
Appellant(s): MAHLER ET AL.

Christopher E. Aniedobe
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 20 November 2008 appealing from the Office action mailed 17 December 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: Claim 51 is a canceled claim and as such any rejection of claim 51 has been rendered moot by the cancellation of claim 51 as per the claim amendments received October 19, 2007 which were entered.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 99/16467	Valenta et al.	4-1999
US 6,187,311	Nishiyama et al.	2-2001

Vrtala et al., "T Cell Epitope-Containing Hypoallergenic Recombinant Fragments of the Major Birch Pollen Allergen, Bet v 1, Induce Blocking Antibodies" J. Immunol. 2000, 165:6653-6659.

Hem et al., "Structure and Properties of Aluminum-Containing Adjuvants", chapter 9 of Vaccine Design: The Subunit and Adjuvant Approach, Plenum Press, 1995, pages 249-276.

Blumenthal et al., "Definition of an Allergen (Immunobiology)" chapter 2 of Allergens and Allergen Immunotherapy, 3rd edition, 2004, Marcel Dekker, Inc., pages 37-50.

Lockey et al., "Tree Pollen Allergens" in Allergens and Allergen Immunotherapy, 3rd edition, 2004, Marcel Dekker, Inc., chapter 10, pages 165-184.

Breiteneder et al., "Four recombinant isoforms of Cor a I, the major allergen of hazel pollen, show different IgE-binding properties" Eur. J. Biochem., 1993, 212:335-362.

Bohle et al., "Characterization of the T cell response to the major hazelnut allergen, Cor a 1.04: evidence for a relevant T cell epitope not cross-reactive with homologous pollen allergens" Clin Exp Allergy, 2005, 35:1392-1399.

Norman, P.S., "Current status of immunotherapy for allergies and anaphylactic reactions" Advances in Internal Medicine, 1996, 41:681-713.

Malling H.J., "Immunotherapy for allergic Rhinoconjunctivitis" chapter 26 of Allergens and Allergen Immunotherapy, 3rd edition, 2004, Marcel Dekker, Inc., pages 495-509.

Niederberger et al. "Recombinant birch pollen allergens (rBet v 1 and rBet v 2) contain most of the IgE epitopes present in birch, alder, hornbeam, hazel, and oak pollen: a quantitative IgE inhibition study with sera from different populations" J Allergy Clin Immunol 1998, 102:579-591.

Mahler et al., "Vaccines for birch pollen allergy based on genetically engineered hypoallergenic derivatives of the major birch pollen allergen, Bet v 1" Clin Exp Allergy, 2004, 34:115-122.

Burks et al., "Mapping and mutational analysis of the IgE-binding epitopes on Ara h 1, a legume vicilin protein and a major allergen in peanut hypersensitivity" 1997, Eur J Biochem 245:334-339.

Reese et al., "Reduced allergenic potency of VR9-1, a mutant of the major shrimp allergen Pen a 1 (tropomyosin)" J Immunol 2005 175:8354-8364.

Vrtala et al., "Conversion of the major birch pollen allergen, Bet v 1, into two nonanaphylactic T cell epitope containing fragments" J Clin Invest 1997 99:1673-1681.

Vrtala et al., "Genetic engineering of the major timothy grass pollen allergen, Phl p 6, to reduce allergenic activity and preserve immunogenicity" J Immunol, 2007, 179:1730-1739.

Orlandi et al., "The recombinant major allergen of *Parietaria judaica* and its hypoallergenic variant: in vivo evaluation in a murine model of allergic sensitization" Clin Exp Allergy 2004, 34:470-477.

Von Garnier et al., "Allergen-derived long peptide immunotherapy down-regulates specific IgE response and protects from anaphylaxis" Eur J Immunol, 2000, 30:1638-1645.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 33, 34, 37-41, 43-46 48-50, and 52-54 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating birch allergy by administering trimers of Bet v 1, administering amino acid fragment 1-73 of Bet v 1, or amino acid fragment 74-159 of Bet v 1, does not reasonably provide enablement for the treatment or prevention of IgE mediated disorders resulting from exposure to the major allergens of alder, birch, and hazel by administering derivatives of Bet v 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has broadly claimed a method of treating or preventing IgE-mediated allergic disorders resulting from exposure to the major allergens of alder, birch and hazel by repeatedly administering derivatives of Bet v 1. To support such methods, applicant has disclosed an in vivo model wherein trimers of Bet v 1, amino acids 1-73 of Bet v 1, and amino acids 74-159 of Bet v 1 are administered to mice such that the mice generate an antibody response that blocks the binding of IgE from birch pollen allergic patients to native Bet v 1 allergen (see particularly Examples 2 and 5). It is the crosslinking of IgE present on the surface of mast cells and basophils (the IgE is pre-bound to the high affinity receptor $Fc\varepsilon RI$) by specific allergen that causes the release of

soluble mediators such as histamines that cause the commonly recognized signs and symptoms of an allergic reaction. Thus, the induced blocking antibodies bind to the native allergen before the allergen can be bound by IgE, owing to the much larger concentration elicited blocking antibodies as compared to IgE and because the antigenic epitopes recognized by the blocking antibodies are structurally distinct from the epitopes recognized by IgE such that binding of the blocking antibodies to the allergen sterically hinders the binding of IgE to the allergen.

Applicant's claimed invention recites methods of treating or preventing an IgE-mediated allergic disorder, but the specification does not appear to define the term prevent. Allergic reactions occur subsequent to allergen reexposure, and as such one reasonable interpretation of "prevention" is that therapy needs to be initiated prior to reexposure to the allergen such that the development of an allergen specific IgE response never occurs. Another reasonable interpretation of "preventing" is that the therapeutic method is 100% effective in 100% of patients.

The development of an allergen specific IgE response is due to the complex interplay of environmental and genetic factors, and therefore it is not predictable who will or will not develop an allergic response to a given allergen (Blumenthal et al., chapter 2 of Allergens and Allergen Immunotherapy, third edition, 2004, pages 37-50, see entire document particularly pages 42-46, Figure 2, and the salient points section spanning pages 47 and 48). The claims recite that the allergen derivative is to be administered to a patient in need thereof, but as discussed above it is unpredictable who will or will not develop an IgE-mediated disorder specific for a given allergen. As such the only identifiable patients in need of treatment are those already known to suffer from allergies specific for a given allergen. These patients currently have an ongoing IgE-mediated immune response directed to the specific allergen, and as such the IgE-mediated reaction cannot be prevented because it has already occurred. Given the unpredictability in who will or will not develop an allergic reaction as taught by Blumenthal et al., it is unlikely that any specific therapy will be effective in all patients.

While it is known that epitope crossreactivity is common among homologous alder, birch and hazel pollen allergens, unique epitopes can be found that are not

present in the genus of all Fagales (which includes birch, alder, and hazel) pollens and as such crossreactivity of a derivative is not guaranteed (Breiteneder et al. and Bohle et al., see entire documents). Further, specific immunotherapy is not effective in all patients, and even when treatment is clinically effective, the majority of patients demonstrate decreased severity of IgE mediated disorders, rather than the prevention and complete cessation of IgE-mediated disorders (Norman, PS, see entire document particularly the paragraph spanning pages 681 and 682, and Malling HJ, see entire document, particularly page 497).

Additionally, the claims recite the prevention of allergy mediated by exposure to the major allergens of alder, hazel or birch by administering a derivative of Bet v 1. It is known in the art that Bet v 1 is a major allergen of birch pollen, but Bet v 1 is not the only major allergen present in birch pollen, as other structurally unrelated allergens, such as Bet v 2, are also found in birch pollen (Niederberger et al. (J. Allergy Clin Immunol 1998; 102:579 - 91 and chapter 10 of Lockey et al). As such, administering a derivative of Bet v 1 would not reasonably be expected to induce a blocking antibody response that was specific for other major birch pollen allergens, such as Bet v 2. As such, a patient would still exhibit the signs and symptoms of an allergic response subsequent to exposure to birch pollen (which is a complex mixture of allergens) because only responses to Bet v 1 are reasonably attenuated by antibodies elicited against a "derivative" of Bet v 1. Thus, prevention of allergic disorders is not reasonably achievable by practicing the invention as presently recited.

The claims recite that the administered agent is a derivative of Bet v 1, a naturally occurring allergen, and in the paragraph spanning pages 2 and 3 of the specification it is disclosed that derivatives of an allergen can be fragments, oligomers, and chemically modified forms of naturally occurring allergens as well as molecules obtained by site directed mutagenesis of an allergen protein.

Polypeptide derivatives of specific allergens are known in the art, and applicant has provided examples of three derivatives of Bet v 1, namely a trimer of Bet v 1, the polypeptide consisting of amino acids 1-73 of Bet v 1, and the polypeptide consisting of amino acids 74-159 of Bet v 1 to support the claimed invention. All three of these

derivatives are known to comprise decreased allergic activity as measured by histamine release and skin prick testing as disclosed by Valenta et al. (WO 99/16467, of record, see entire document).

However, there currently is no art recognized method to distinguish allergic from non-allergic molecules (such as derivatives comprising fragments and oligomers of allergens) on an a priori structural basis (Blumenthal et al., see particularly the last sentence of the third complete paragraph of page 39). If the identity of the IgE binding epitopes that give rise to the allergic activity of an allergen are precisely known, it is not predictable as to which amino acid positions within an epitope need to be altered by site directed mutagenesis such that IgE binding is abrogated (Burks et al., Eur. J. Biochem., 1997, 245:334-339, see entire document, particularly the top right column of page 338). Even when a precise amino acid within in the epitope to be altered is identified, the choice of what that amino acid should be mutated to by site directed mutagenesis is not predictable since some substituted amino acids reduce IgE binding while others have no effect or unexpectedly increase IgE binding (Nishiyama et al., US Patent 6,187,311, see entire document, particularly lines 4-30 of column 3, and Reese et al., J. Immunol., 2005, 175:8354-8364, see entire document, particularly the paragraph that spans pages 8357 and 8358, Table I and Figure 2). The specification does not appear to teach what changes are to be made in Bet v 1 to make derivatives that satisfy the recited functional criteria (excepting the working examples of Bet v 1 trimers and amino acid fragments 1-73 and 74-159), and the teachings of the art indicate that the structure of the material obtained as an immunotherapeutic agent comprising reduced allergenic activity at the conclusion of a screening protocol cannot be predicted. Given the above, it appears that a skilled artisan would need to rely on trial and error to identify derivatives suitable for use in the recited method. Trial and error by definition is random and unpredictable, and therefore a skilled artisan would need to perform an undue amount of research prior to practicing the full breadth of applicant's claimed method.

Therefore, given the breadth of the instant claimed invention, the amount of guidance and working examples disclosed in the specification, and the teachings of the

art, a skilled artisan would be unable to practice the full breadth of applicant's claimed invention without conducting an undue amount of additional research.

B. Claims 33, 34, 37-41, 43-46, and 48-50 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Appellant has claimed methods of treating or preventing an IgE-mediated allergic disorder resulting from exposure to the major allergens of alder, hazel and birch by repeatedly administering one or more immunotherapeutic agents derived from Bet v 1 to a patient. The administered "agents" are further recited to comprise an allergenic activity that is 50% or less as compared to the naturally occurring Bet v 1 allergen. To support this genus of "agents" the specification has disclosed three examples, namely a trimer of Bet v 1, the polypeptide consisting of amino acids 1-73 of Bet v 1 and the polypeptide consisting of amino acids 74-159 of Bet v 1. This disclosure does not support the claimed genus for the reasons set forth below.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

Note that in The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court held that disclosure of a single member of a genus (rat insulin) did not provide adequate written support for the claimed genus (all mammalian insulins), and that the genus of all mammalian insulins is more structurally

similar than the genus comprising all derivatives of Bet v 1 given appellant's definition of the term "derivative". In this same case the court stated, "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene ("derivative") does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes ("derivatives") may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As previously indicated, appellant has claimed methods of treatment and prevention of allergies caused by the major allergens of alder, hazel, and birch by administering a derivative of Bet v 1. Note that there are many "major allergens" of birch pollen in addition to Bet v 1, such as Bet v 2 and others (Niederberger et al., J. Allergy Clin Immunol 1998; 102:579 - 91 and chapter 10 of Lockey et al). The specification defines "derivatives" in the paragraph spanning pages 2 and 3 of the specification to be fragments, oligomers, and chemically modified forms of naturally occurring allergens as well as molecules obtained by site directed mutagenesis of an allergen protein. The specific "derivatives" used as "agents" in the instant claims minimally comprise an allergenic activity that is 50% or less as compared to naturally occurring Bet v 1. It is known that allergic symptoms are mediated by IgE, and that

antigen specific immunotherapy works by inducing an IgG response in an individual that is of sufficient magnitude that the induced IgG is able to outcompete (block) preexisting IgE in the patient for binding to the allergen in question. Thus, the claims require that the administered "agent" elicit an antibody response that is capable of inducing an antibody response specific for the major allergens of alder, hazel and birch. Note that the instant claims recite administering a composition comprising a derivative of Bet v 1, a singular allergen from birch pollen, wherein the derivative comprises very specific properties as discussed above.

As is discussed above, the term "derivative" has been defined very broadly. The specification comprises three examples, two of which are truncations of the natural allergen (aa1-73 and aa74-159) and one which is a trimer of the naturally occurring Bet v 1 allergen. Given that the definition of "derivative" is not limited to oligomers and truncations, the disclosed species are not structurally representative of full breadth of the recited genus. Further, the "derivatives" used in the claimed methods are recited as comprising specific functional activity limitations. The specification does not teach how the recited functional properties are correlated with structure of the disclosed species. Further, the art teaches that correlations between structure and IgE binding (or the lack of IgE binding) cannot be predicted on an a priori structural basis (Blumenthal et al. in Allergens and Allergen Immunotherapy, 3rd edition, 2004, pages 37-50, see entire document, particularly the last sentence of the third complete paragraph of page 39). As such, the disclosure of the polypeptides consisting of amino acids 1-73 and consisting of amino acids 74-159 of Bet v 1 and trimers of Bet v 1 do not comprise a representative number of the genus of derivatives recited in the instant claims. Since the instant specification fails to provide adequate written description for the genus of "derivatives" recited in the instant claimed methods, it logically follows that methods of administering said 'derivatives" also lacks adequate written description in the specification, and therefore appellant was not is possession of the instant claimed methods at the time the instant application was filed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

C. Claims 33, 34, 37-40, 43-46, 48, 49, 53 and 54 stand rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

Vrtala et al. teach methods of specific immunotherapy to treat birch allergy by administering derivatives of Bet v 1 (see entire document, particularly the abstract and the left column of page 6658). The administered derivatives induced the production of antibodies which precluded the binding of IgE antibodies to native Bet v 1 allergen (see particularly the abstract and Tables II-IV). The derivatives of Bet v 1 are taught as being repeatedly administered at the same concentration at intervals greater than 14 days, with such administrations occurring four times (see particularly the second and third paragraphs of the right column of page 6654). Administered dosages are taught as comprising 5 μg and 200 μg of Bet v 1 derivatives (ibid.). These dosages are further

taught as being adsorbed onto an adjuvant (ibid. and the last sentence of the first full paragraph of the left column of page 6658).

Note that claims 53 and 54 recite administering peptides consisting of amino acids 1-73 or 74-159 of Bet v 1. The specification indicates on page 8 that the recombinant Bet v 1 fragments used in the instant specification are the peptides disclosed in the 1997 J. Clin. Invest. article by Vrtala et al. In this 1997 article, Vrtala et al. teach how to make recombinant Bet v 1 fragments consisting of amino acids 1-74 and 75-160 of Bet v 1. Note that the 2000 J. Immunology paper by Vrtala et al. that forms the basis of this rejection discloses the use of Bet v 1 fragments consisting of amino acids 1-74 and 75-160, and references the 1997 J. Clin. Invest. paper in the materials and methods section for details concerning the manufacture of said peptides. When this numbering discrepancy was brought to the attention of appellant, the response received from appellant on October 19, 2007 states that the Bet v 1 fragments disclosed by Vrtala et al. are indeed the same fragments as those recited in instant claims 53 and 54 (see the paragraph spanning pages 8 and 9 of the 10/19/07 response).

It is noted that the Bet v 1 derivatives of Vrtala et al. were administered to model organisms, namely mice and rabbits. However, given their disclosure that the Bet v 1 derivatives are to be used for immunotherapy and that clinical trials are to be conducted, a skilled artisan would immediately envisage administering the Bet v 1 derivatives to humans. Alternatively, a person of ordinary skill in the art would have been motivated to administer the Bet v 1 derivatives to humans because Vrtala et al. specifically disclose that their derivates are to be used for immunotherapy, comprise advantageous properties such as reduced side effects, and that they are planning a clinical trial involving the administration of their derivatives (see particularly the two full paragraphs of the left column of page 6658). As such, administering the derivatives to humans is merely doing what Vrtala et al. plan to do but have not yet done. A person of ordinary skill in the art would have a reasonable expectation of success in treating

humans based on the success of the method in two distinct animal models, namely mice and rabbits.

D. Claims 33, 34, 37, 46, 48-50, 52-60 stand rejected under 35 U.S.C. 102(b) as being anticipated by Valenta et al. (WO 99/16467 A1) as evidenced by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659)

Valenta et al. teach methods of treating birch allergy by repeatedly administering derivatives of Bet v 1 (see entire document, particularly the abstract and the paragraph spanning pages 5 and 6 and claims 11-16). The Bet v 1 derivatives comprise the polypeptides consisting of amino acids 1-74 of Bet v 1 and amino acids 75-160 of Bet v 1, as well as trimers of Bet v 1 (see particularly lines 9-34 of page 4, Example 1 from pages 6-13, most particularly lines 16-37 of page 13, and Example 3 from pages 15-19, most particularly lines 10-13 of page 19). These polypeptides are taught as being combined with the pharmaceutically acceptable adsorbate and adjuvant aluminum hydroxide (alum) prior to *in vivo* administration (see particularly lines 2-9 of page 6). The trimeric Bet v 1 derivatives of Valenta et al. give at least 10-fold reduced reactions in skin prick tests of allergic individuals while the fragments of Bet v 1 do not appear to comprise any allergenic activity (see particularly lines 3-14 of page 13 and lines 10-13 of page 19). Thus the derivatives disclosed by Valenta et al. comprise "reduced allergenic activity" of 25% or less as compared to the native allergen as per the definition set forth on page 4 of the instant specification.

The derivatives of Valenta et al. are taught to be used for specific hyposensitization therapy in mammals, especially humans, wherein hyposensitization involves the generation of an IgG immune response that binds the native allergen (see particularly the paragraph spanning pages 5 and 6). Valenta et al. do not explicitly state that the IgG response that is achieved as part of their hyposensitization methods is an IgE-blocking antibody response, although they do teach that these fragments comprise epitopes known to be bound by monoclonal antibodies that inhibit the binding of allergic patient IgE to native Bet v 1 (see particularly lines 20-34 of page 15). However, it is

inherent that an immune response which precludes binding of IgE to the native allergen occurs upon administration of the Bet v 1 derivatives disclosed by Valenta et al. This is because Vrtala et al. teach that administration of the same derivatives as taught by Valenta et al. induce a blocking antibody response (see entire document, particularly the abstract, discussion, and Tables II and III). Further, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)." Note that the induction of an IgE-blocking response is a scientific explanation for why the derivatives of Valenta et al. are effective in methods of immunotherapy.

Additionally, claims 53, 54, 57, 59, and 60 are included in this rejection because Example 3 of Valenta et al. discloses that the Bet v 1 fragments used in their example are the Bet v 1 fragments disclosed by Vrtala et al. in their 1997 J. Clin. Invest. paper. As was discussed above in conjunction with the teachings of Vrtala et al., it appears that the recitation of amino acids 1-73 and 74-159 in the instant specification is a typographical error. This is because the instant specification teaches the '97 Vrtala et al. paper as the source of the peptides used in the examples of the instant specification and the '97 reference clearly teaches fragments 1-74 and 75-160 of Bet v 1 rather than fragments 1-73 and 74-159 of Bet v 1. Appellant has clarified this issue in the response received October 19, 2007 wherein it is stated that the Bet v 1 fragments disclosed by Vrtala et al. (which are the same as the fragments used by Valenta et al.) are indeed the same fragments as those recited in instant claims 53, 54, 57, 59, and 60 (see the paragraph spanning pages 8 and 9 of the 10/19/07response).

Therefore, the prior art anticipates the instant invention.

E. Claims 33, 49, 50, 55, 56, 57, 59, and 60 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-

6659) in view of Hem et al. (chapter 9 of Vaccine Design: The Subunit and Adjuvant Approach, 1995, pages 249-76).

The teachings of Vrtala et al. have been discussed above. While Vrtala et al. teach that their allergen derivatives are to be used in methods of human administration (see entire document, particularly the abstract and discussion sections), these teachings differ from the instant claimed invention in that they do not teach the use of aluminum hydroxide as part of the administered composition.

Hem et al. teach that aluminum hydroxide is a widely used adjuvant that offers the important advantage of being the only adjuvant licensed by the Food and Drug Administration for administration to human patients (see entire document, particularly the introduction).

Therefore, it would have been obvious at the time the invention was made to substitute aluminum hydroxide for the adjuvant used in the methods of administration taught by Vrtala et al. Motivation to make this substitution comes from the teachings of Vrtala et al. that their allergen derivative compositions are to be administered to humans and the teachings of Hem et al. that the only adjuvant that can be administered to human patients is aluminum hydroxide.

Further, claim 56 recites that the composition comprising aluminum hydroxide is administered such that the time interval between the third and fourth administrations is lengthened. While Vrtala et al. do not teach that the time interval between the third and fourth administrations is longer than the time interval between the first three administrations, it would have been obvious to a person of ordinary skill in the art at the time the invention was made modify the interval between administrations. A person of ordinary skill in the art at the time the invention was made would have been motivated to modify the time intervals to optimize the treatment method, and determining the optimal intervals of administration of the allergen derivative is well within the purview of one of ordinary skill in the art at the time the invention was made. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re*

Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05 part II A.

F. Claims 33, 38, and 41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

The teachings of Vrtala et al. have been discussed above. These teachings differ from the instant claimed method in that while Vrtala et al. teach repeated administration of allergen derivatives wherein the period between administrations is at least 14 days, Vrtala et al. do not teach that the time interval between the third and fourth administrations is longer than the time interval between the first three administrations. However, it would have been obvious to a person of ordinary skill in the art at the time the invention was made modify the interval between administrations. As person of ordinary skill in the art at the time the invention was made would have been motivated modify the time intervals to optimize the treatment method, and determining the optimal intervals of administration of the allergen derivative is well within the purview of one of ordinary skill in the art at the time the invention was made. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05 part II A.

G. Claims 33, 38-41, 43-45, and 56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Valenta et al. (WO 99/16467 A1).

The teachings of Valenta et al. have been discussed above. These teachings differ from the instant claimed method in that while Valenta et al. teach repeated administration of allergen derivatives, Valenta et al. do not teach specific administration timings or dosage amounts. However, it would have been obvious to a person of ordinary skill in the art at the time the invention was made modify the treatment methods of Valenta et al. given that it is well within the purview of skilled artisans to determine suitable dosages and timings for the treatment of their patients. Further, it has been

held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05 part II A. As such, specific dosages and timings of administered agents do not generally impart novelty or nonobviousness to a claimed invention, especially in the absence of evidence to the contrary. Note that there does not appear to be any evidence of record to indicate that the recited dosages and timings are not obvious and could not be obtained by routine optimization.

(10) Response to Argument

A. Appellant's arguments filed November 20, 2008 have been fully considered but they are not persuasive. Appellant's first ground of argument is that the construction of "prevent" as set forth in the rejection of record is scientifically untenable and therefore unreasonable.

This argument is not persuasive. Appellant did not define the term "prevent" in the instant specification, and thus the rejection of record sets forth the possible ways in which this term may be interpreted by skilled artisans as well as rationales for why the invention as currently recited may be capable to treating birch allergy but is not capable of preventing said allergy. Appellant argues that since no therapeutic method is 100% effective, this interpretation is unreasonable. However, the specification provides no guidance or direction to what appellant would consider reasonable. Is it reasonable to expect that a method of "prevention" works 90% of the time, or only 50% of the time, or maybe even only 5% of the time? The specification does not answer this question, and as was cited in the rejection of record, the art of Norman and Malling indicate that while allergy suffers exhibit reduced symptoms subsequent to immunotherapy, their symptoms are not entirely eliminated or "prevented". Given that the specification does not define how the term prevent is to be interpreted and that the art indicates that allergy symptoms are alleviated rather than eliminated by immunotherapy, it is reasonable that the claimed methods would treat, but not eliminate/prevent allergy

symptoms. Further, given that antibodies are antigen specific, that there are multiple major allergens of birch, alder, and hazel, and the recitation that the claims need only comprise a single derivative of Bet v 1, "prevention" is also not reasonable since while subsequent to administration, a patient may develop blocking antibodies that bind Bet v 1, these same antibodies are not reasonably expected to bind other major allergens, such as Bet v 2. As such, when a patient encounters birch pollen, the immune response to these other allergens is not diminished and thus the patient will still suffer the signs and symptoms of an allergic response.

Appellant's second ground of argument is that "the cross-reactivity of derivatives of Bet v 1 with Alder and Hazel allergens is a settled proposition and that it is reasonable to expect a derivative of Bet v 1 will induce blocking antibodies which comprise substantial cross reactivity."

This argument is not persuasive. As was detailed in the rejection, crossreactivity is not guaranteed as per the disclosures of Breiteneder et al. and Bohle et al. (of record). The claims recite administering a Bet v 1 derivative to treat IgE mediated disorders arising from exposure to the major allergens of alder, hazel and birch. Even as stated in appellant's 10/19/2007 reply: "As far back as 1989, Niederberger et al. ... observed that recombinant birch pollen allergens contain most of the IgE epitopes present in birch, alder, hornbeam, hazel, and oak pollen."

The recombinant allergens disclosed by Niederberger et al. were full length Bet v 1 and Bet v 2. The instant claims are not limited to full length molecules, but instead recite derivatives only of Bet v 1 encompassing small peptides formed by truncation, as well as mutated polypeptides of any size, oligomers of any size, and chemically modified versions of all of the aforementioned derivatives formed via undisclosed chemical means (see the paragraph spanning pages 2 and 3 of the specification). If even the full length molecule comprises only most, but not all, IgE epitopes, it is not reasonable that even shorter sequences will comprise 100% crossreactivity. Further, even assuming *in arguendo* that a Bet v 1 derivative will induce blocking antibodies that also bind the homologous polypeptide antigen found in alder and hazel pollen, these antibodies will still not bind other major allergens found in pollen, such as Bet v 2.

Appellant's third ground of argument is that "the claimed methodology is heuristic and the examiner failed to appreciate the fundamental nature of the claims".

This argument is not persuasive. Appellant states the belief that the invention is a rapid, easily attainable method of discovering and using Bet v 1 derivatives, and that this can be done by injecting a derivative of Bet v 1 into a test animal and observing if the "derivative" does or does not meet the limitations of inducing a blocking antibody response and comprising reduced allergenicity without any foreknowledge of the structure or components contained within said derivative. However, appellant has claimed a method of treatment, not a screening method. As such, the claims require that something known to meet the recited functional limitations be administered to the patient. Appellant's characterization of the screening assay disclosed in the specification appears to be select anything at random, inject it into an animal, and see if it worked. Thus, the amount of guidance and direction concerning what is to be used as a starting material in the screening assay is minimal, and as has been discussed above the genus of "derivatives" is quite broad and allergenicity cannot be reasonably predicted. Thus, a skilled artisan attempting to practice the claimed method using a "derivative" that is other than a Bet v 1 trimer or aa1-73 and aa74-159 of Bet v 1 would be forced to generate a large number of "derivatives" without any reasonable expectation that they would work prior to administration. This level of trial and error does not appear to provide sufficient guidance and direction as to how to make the "derivatives" recited in the instant claims and thus methods of using said derivatives are not reasonably enabled.

B. Appellant's arguments filed November 20, 2008 have been fully considered but they are not persuasive. Appellant's first ground of argument is that no correlation is required between the recited functional properties of the Bet v 1 derivative and the structure of said derivative since the claimed method can be practiced without knowing the structure of what is being administered.

Appellant is correct that adequate written description can be provided in the specification by methods other than a correlation between structure and function, such

as by disclosing a representative number of species. As was discussed in the rejection of record, the instant specification does not establish a correlation between structure and function nor does it disclose a representative number of species within the recited genus since said genus is large and structurally diverse such that the three disclosed examples do not encompass the breadth of "derivatives". With regard to the correlation between structure and function, prior office actions rebutting appellant's arguments state the following:

> Applicant's arguments filed January 29, 2007 have been fully considered but they are not persuasive. Applicant argues that "The written description requirement has been met in this case by disclosure of relevant identifying characteristics - namely that the candidate therapeutic agents of this invention are those which upon injection into an immunological model elicit both IgE-blocking antibodies production and also have reduced allergenicity compared to wild-type allergens. This identifying characteristic, without more, has given possession to the Applicants, as at the filing date, of treatment methods using the results of the elegant in vivo screening methodology of the present invention."
>
> This argument is not persuasive because the instant specification does not disclose how the structure of the derivative is correlated with the functional properties of eliciting IgE-blocking antibodies and reduced allergenicity. Even if a skilled artisan could obtain derivatives using a screening assay, the structure of derivatives that comprise the desired functional properties would not be known until such time as the screening assay is completed. How can the specification provide adequate written description for a derivative that cannot be known until the completion of a screening method that has yet to be performed? Note that in Univ. of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (Fed.Cir. 2004) the court held that the disclosure of a screening assay and the recitation of functional properties of molecules obtained upon completion of said screening assay did not provide adequate written description for the molecules themselves. More specifically, the court held that patented claims which encompassed methods of treatment with undiscovered Cox-2 inhibitors such as Celebrex were invalid for lack of possession of the genus of administered Cox-2 inhibitors.
>
> The instant case is similar in that the specification provides a screening assay and recites functional properties of allergen derivatives that are yet to be discovered. Further, the three Bet v 1 derivatives that are disclosed (trimer, amino acids 1-73 and amino acids 74-159) are not representative species of the genus of all major allergens of alder, hazel, and birch.

Appellant argues that allergen extracts are routinely used without performing a structural characterization of the components.

This argument is not persuasive since the claims to not recite administering extracts but rather recite administering derivatives. The term derivative as has been discussed in the rejection of record is broad and encompasses many structurally distinct species. Birch pollen extracts, such as those used in immunotherapy, generally compose full length allergen polypeptides and do not encompass the breadth of what appellant has defined derivatives to be in the instant specification.

Appellant further argues that "the claimed methodology is inherently self-validating and the methodology does not stand or fall on the exact molecularity of the hybrid polypeptides or derivatives thereof." Appellant states "If the Applicants were claiming a product, then adequate inquiry must be had as to whether they had the claimed product in their possession as at the time of filing of the Application. On the other hand, if the Applicants are claiming a method, then the inquiry as to whether they had possession of the method as at the filing of the Application need not exceed the metes and bounds of the claimed method; especially where as here, those metes and bounds have been clearly and concisely delineated." Appellant then goes on to argue that "In regards, therefore, to the heuristic nature of the claimed invention, it is clear and manifest error to insist that guidance as to molecularity of species amenable to the methodology, other than the restrictions appearing on the face of the invention, be provided, where as here, the invention itself is self-validating. In other words, however derived, and whatever the molecularity, be it a two amino-acid sequence or five-hundred amino acid sequence, a Bet v 1 derivative can now, by virtue of this invention, be for the first time, routinely tested as candidate immunotherapeutic agents by administering said polypeptide to a test animal and selecting as immunotherapeutic agents those fusion polypeptides that induce IgE-blocking antibodies and has 50% or less reduced allergenicity compared to wild type allergens."

This argument is not persuasive because appellant's claims are therapeutic methods comprising the active step of administering a derivative of Bet v 1 to a patient. As such, in order to practice the full breadth of the claimed invention, an artisan must first be in possession of that which is being administered. If the artisan is not in possession of the derivative, how can the administration step be practiced? Appellant's

arguments concerning the nature of the screening assay are not relevant because appellant has not claimed a screening assay.

C. Appellant's arguments filed November 20, 2008 have been fully considered but they are not persuasive. Appellant argues that the examiner has engaged in impermissible hindsight to misconstrue the teachings of the prior art. Specifically, four enumerated points are argued by appellant as being patentable differences between Vrtala et al. and the instant invention. As quoted directly from pages 28 and 29 of the brief, these are:

> 1. Vrtala et al. (2000) only uses specifically identified Bet v 1 fragments and thus fails to demonstrate the general principles of the immunotherapeutic utility of a broad range of Bet v 1 allergens including fragments AND oligomers.
>
> 2. Vrtala et al. (2000) dealt with only the isolated fragments and not the fragment mix for vaccination;
>
> 3. Vrtala et al. (2000) uses mainly complete and incomplete Freunds Adjuvant (CFA, ICFA) which is not allowed for human use and it has been recently demonstrated that hypoallergens given with CFA fail to induce allergen-specific IgG when adsorbed to Alum (See Vrtala et al. (2007) J. Immunol. 179:1730-1739. This also puts paid to the Examiner's argument that it would have been obvious to merely substitute Alum with CFA.
>
> 4. The recited dosage levels and the periodicity schedule are not subject to routine optimization. On the contrary, it is experimentally intensive and critical to successful immunotherapy.

Each of these points will be discussed in turn.

First, all of the instant claimed methods of treatment recite administering "one or more" derivatives of Bet v 1. As evidenced by instant claims 53, 54, 57, and 59, and appellants' statements on the record detailed in the rejection of record indicate that the fragments of Bet v 1 used in the methods of Vrtala et al. are the same fragments that are recited in the instant methods. Thus, the claims require administration of only a single agent, and such an administration has been performed on mice and rabbits as

detailed in Vrtala et al. It is well known that disclosure of a species anticipates the genus to which the species belongs, and thus the teachings of the prior art anticipates that which is instantly claimed. With regard to oligomers of Bet v 1, claims that are limited to only administering fragments are not part of this rejection.

Second, as discussed above, the claims recite administering "one or more". Thus, the alleged failure to disclose vaccination with a mix of fragments by Vrtala et al. is not material since it is a limitation that is not recited in the claims. However, as was communicated to appellant in prior office actions, given that the two peptides of Vrtala et al. were both disclosed as being useful in treating allergy, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to mix then together for administration for the treatment of allergy. Note that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See MPEP 2144.06. Note that as discussed above, the instant claims do not require administration of more than one derivative of Bet v 1.

Third, the claims instantly rejected do not recite administration with an adjuvant, and as discussed in the rejection of record, Vrtala et al. explicitly state that they will be conducting clinical trials using their disclosed fragments (see particularly the abstract and the last paragraph on page 6658). Thus, a person of ordinary skill in the art would have clear motivation to treat humans and have a reasonable expectation of success in doing so based upon successful administration in both the mouse and rabbit model systems. Note that claims reciting administration in alum have been rejected in a separate 103 rejection, and thus appellant's comments concerning the obviousness of substituting one adjuvant for another adjuvant are more pertinent and will be more full addressed with regards to ground of rejection E.

Fourth, the dosages recited in the instant claims are disclosed in the prior art. Specifically, the instant claims recite "at least 5 μg" and at least 10 μg". The prior art discloses administering 5 mg (mouse) and 200 mg (rabbit), thus meeting the instant claim limitations (see particularly the right column of page 6654). With regards to periodicity, the instantly rejected claims recite "periodically administering for a number of times", with dependent claims reciting the limitations of "a period of 14 days between administrations" and that the derivative is administered "between 3 to 5 times" or is administered 4 times. Vrtala et al. state on page 6654 that mice were administered the Bet v 1 derivatives monthly, and that four administrations took place. Note that a month is longer than 14 days.

D. Appellant's arguments filed November 20, 2008 have been fully considered but they are not persuasive. Appellant argues as follows in the brief:

> The foregoing arguments are incorporated herein by reference. For at least the patentable differences between Vrtala et al. and the instant invention, there is no basis for this ground for rejection. Specifically, the Valenta reference refers to the hyposensitization of patients using in general, polymeric forms of hypo-allergenic fragments of naturally occurring allergens. While Valenta et al, illustrates the principle that polymeric fragments of naturally occurring allergens can have immunotherapeutic potentials, nothing is mentioned in Valenta et al of the periodicity element of claim 33 nor was the "50% or less" hypoallergenic activity established as a therapeutic threshold.

Given that the "foregoing arguments" specifically identify the teachings of Vrtala et al. and why appellant believes that the claims are patentably distinct from the disclosure of Vrtala et al., and given that Vrtala et al. and Valenta et al. are distinct documents, it is not clear what argument(s) appellant is trying to make. However, as far as periodicity elements are concerned, the following was previously communicated to appellant as part of a prior office action.

> The "periodicity element" recited in independent claim 33 is "comprising periodically administering for a number of times". The paragraph spanning pages 5 and 6 of Valenta et al. discloses:

> The second aspect of the invention is specific hyposensitization therapy. This therapy may be performed as known in the art for protein allergens and encompasses administering repeatedly to the mammal, typically a human individual, suffering from type I allergy against the protein allergen an immunogen that is capable of raising as IgG immune response against the protein allergen. Administration may be done systemically, for instance by injection, infusion, etc., but also the oral route has been suggested in order to expose the intestinal part of the immune system. The immunogen may be admixed with suitable adjuvants such as aluminium oxide. See further Norman P S, "Current status of immunotherapy for allergies and anaphylactic reactions" Adv.Internal. Medicine 41 (1996)681 713.
>
> Given that the allergen is administered repeatedly (i.e. multiple times), said administrations must occur over an interval of time, thus providing a "periodicity element". Further, the art of Norman cited by Valenta et al. teaches that it is known in the art that administrations are repeatedly given over a period of time, often years (see entire document, particularly pages 681 and 698).

Further, page 11 of Valenta et al. discloses a working example comprising monthly administrations of 5 μg of Bet v 1 trimers to mice. Also, appellant's characterization of Valenta et al. as "hyposensitization of patients using in general, polymeric forms of hypo-allergenic fragments" is misleading in that it should be pointed out that Example 3 beginning on page 14 of Valenta et al. deals with non-oligomeric Bet v 1 fragments aa1-74 and 1175-160 as detailed in the rejection or record, while oligomeric trimers of Bet v 1 are discussed in Example 1. Thus, the disclosure of Valenta et al. is more extensive than appellant's characterization of the prior art.

With regard to the 50% or less activity limitation, claim 52 recites trimers of Bet v 1, and this claim is dependent from claim 33 which recites allergenic activity of 50% or less. Valenta et al. made trimers of Bet v 1 used them in methods of administration. As evidenced by dependent claim 52, it is inherent that trimers of Bet v 1 comprise the recited activity. Appellant has provided no evidence that the trimers of Valenta et al. and the instant invention were made by different methods, and a comparison of page 8 of the instant specification and Example 1 of Valenta et al. finds that both trimers were made in E. coli BL21 cells that had been transfected with plasmid pET-17b into which a

trimeric Bet v 1 construct had been inserted. Thus, the prior art constructs and those of the instant specification appear to have been generated in an identical manner.

E. Appellant's arguments filed November 20, 2008 have been fully considered but they are not persuasive. Appellant argues in the brief that "The foregoing arguments are incorporated herein by reference. For at least the patentable differences between Vrtala et al. and the instant invention, there is no basis for this ground for rejection."

The foregoing arguments have been addressed supra, and will not be elaborated further excepting for the obviousness of substituting adjuvants in methods of administration. As has been briefly touched on supra, appellant also argues point 3 which is that "Vrtala et al. (2000) uses mainly complete and incomplete Freunds Adjuvant (CFA, ICFA) which is not allowed for human use and it has been recently demonstrated that hypoallergens given with CFA fail to induce allergen-specific IgG when adsorbed to Alum (See Vrtala et al. (2007) J. Immunol. 179:1730-1739. This also puts paid to the Examiner's argument that it would have been obvious to merely substitute Alum with CFA."

This argument is not persuasive because the evidentiary reference argued by appellant, Vrtala '07, discloses administration of an allergen that is not Bet v 1 and discloses that one of the fragments when absorbed onto alum *did* induce allergen specific IgG (see entire document, particularly sentence 6 of the abstract). Further, the art demonstrates numerous examples wherein administering hypoallergenic derivatives in alum induces an IgG response. See Orlandi et al., particularly the abstract, the right column of page 474, and Figure 4, as well as von Garnier et al., see particularly the abstract, the left column of page 1643, and Figure 1. As such, the use of compositions comprising allergen derivatives in alum to obtain IgG responses was well known in the art at the time the invention was made. See also the disclosure of Valenta et al. (WO 99/16467, of record) wherein derivatives of Bet v 1 are disclosed in compositions comprising alum for administration to humans.

F. Appellant's arguments filed November 20, 2008 have been fully considered but they are not persuasive. Appellant argues in the brief that "The foregoing arguments are incorporated herein by reference. For at least the patentable differences between Vrtala et al. and the instant invention, there is no basis for this ground for rejection."

This is not persuasive for reasons previously communicated to appellant in a prior office action. Briefly, Vrtala et al. disclose that a blocking antibody response can be obtained in a patient subsequent to monthly administrations of their Bet v 1 fragments. As such, the general conditions of the claims (i.e. periodic administration wherein the period between administrations is greater than 14 days) are taught in the art and *In re Aller* held that when such general conditions are known, optimizing involves only routine skill in the art. Appellant stated on the record as part of the 1/29/07 response that only routine skill is involved ("Applicants understand that a simple and elegant screening procedure of this invention involves routine skill in the art...") but then argued that the exact timing and dosages are not obvious. As stated in the rejection of record, a skilled artisan would be motivated to optimize the protocol of Vrtala et al., and given that such optimization is routine and thus within the skill of an ordinary artisan, the claimed method is obvious. Applicant has supplied only argument, not evidence, to rebut the obviousness rejection of the instant claims. As is discussed in MPEP 2145, attorney argument does not replace the need for evidence when rebutting cases of prima facie obviousness.

G. Appellant's arguments filed November 20, 2008 have been fully considered but they are not persuasive. Appellant argues in the brief that "The foregoing arguments are incorporated herein by reference. For at least the patentable differences between Vrtala et al. and the instant invention, there is no basis for this ground for rejection."

This argument is not persuasive as appellant has not argued anything specifically, and generic arguments have been discussed at length supra.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Michael Szperka/
Primary Examiner, Art Unit 1644

Conferees:

/Eileen B. O'Hara/

Supervisory Patent Examiner

Art Unit 1644

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649